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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,241	WANG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10, 12-30* is/are pending in the application.

4a) Of the above claim(s) *2-10, 12-20, 23, 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,21,22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 1-26, drawn to a system for treating or preventing restenosis providing interventional medical care to a patient in the reply filed on 20 October 2008 is acknowledged. The traversal is on the ground(s) that the examiner has not met the lack of unity of invention requirement that the examiner must (1) list the different groups of claims and (2) explain why each group lacks unity with each other group (i.e., why there is no single general invention concept) specifically describing the unique special technical feature in each group as stated in MPEP 1893.03 (d). This is found persuasive, however, the claims have now been amended to not read upon any of the previously restricted illnesses (see amended claim 1, amendment filed 20 October 2008) therefore the arguments are not applicable to the instant claims as amended by Applicant.

With respect the elected species, applicant has elected with traverse the bioactive agent apoptosis DNA factor. The compound species are drawn to compounds that have distinct chemical compositions and hence different chemical formulas, therefore are not known equivalents in the art and therefore the required election of species is still deemed proper. Applicant has indicated that apoptosis DNA factor reads upon claims 1 and 24-26. Please note that claims 21-22 also read upon apoptosis DNA factor, as evidenced by the instant disclosure in [00140]-[00141]. With regards to the other 2 species requested, upon reconsideration, these 2 species are not deemed necessary for examination.

Claims 2-10, 12-20, 23 and 27-30 are withdrawn as not drawn to the elected Group and/or species. Claims 1, 21-22 and 24-26 are presented for examination on the merits.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. With regards to the priority to provisional application 60/444,391, this provisional application does not contain support for the instantly claimed subject matter "ADF" (apoptosis DNA factor) and therefore the priority for the elected invention goes only back to the priority for the corresponding PCT application, PCT/US04/03143 filed 02/03/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 21-22, 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As discussed in the Guidelines for Examination of Patent Applications under the 35 USC 112, paragraph 1, "Written Description", examination of patent claims for compliance with the Written Description Requirement should include (http://www.uspto.gov/web/menu/written.pdf):

1. A determination as to what the claim as a whole covers. In making this determination, the examiner should consider the full scope of the claim.

In the instant case the claims are drawn to a system for treating a condition by providing interventional medical care to a patient comprising:

a local delivery system;

a bioactive agent;

wherein the local delivery system is adapted to locally deliver the bioactive agent to a region of tissue associated with the condition;

wherein the bioactive agent when locally delivered to the region of tissue is adapted to treat or prevent the condition; and

wherein the bioactive agent comprises **apoptosis DNA factor ("ADF") or an analog or derivative thereof**, or a pharmaceutically acceptable salt thereof, or a combination or blend thereof.

The scope is extremely broad, including any local delivery system, any effect thereof in any tissue, cell, or organism of a bioactive agent comprising apoptosis DNA factor (ADF). Please note that the patent publication of the instant application is referred to. Additionally, with regards to the condition,

2. A full review of the application to understand how the applicant provides support for the claimed invention including each element and/or step. This review includes comparing the claim scope with the scope of the description.

With regards to ADF, the disclosure teaches at [00140]-[00142] that ADF is the fragment of mitochondrial maleate dehydrogenase (MDH) with the following amino acid

sequence: KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYF STPLLLGKKGIEKNLGIGKVSSFEEKMISDAIPELKASIKKGEDFVKTLK (SEQ ID NO: 2).

The disclosure goes on to teach that this compound, and “various appropriate analogs or derivatives thereof”, are considered a further embodiment, however, the disclosure does not expressly provide any definitions for the terms “analog” or “derivative", beyond indicating that: ”further included are certain derivatives or analogs of these compounds, for example, also contemplated is the use of the fragment of ADF with the following amino acid sequence: KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYF STPLLLGKKGIEKNLGIGKVSS (SEQ ID NO: 3)”. The disclosure also teaches that homologs of these compounds are contemplated, in one particular example without limitation, and ADF homolog represented by the substitution of various amino acids giving homologous proteins mediating substantially all of its activity, at least relative to the desired indications described herein.

The specification, at [0088], states: “In the case of polypeptide sequences, which are less than 100% identical to a reference sequence, the non-identical positions are preferably, but not necessarily, conservative substitutions for the reference sequence. Conservative substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine, and leucine; aspartic acid and glutamic acid; asparagine and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine. Thus, included in the invention are peptides having mutated sequences such that they remain homologous, e.g., in sequence, in structure, in function, and in

antigenic character or other function, with a polypeptide having the corresponding parent sequence. Such mutations can, for example, be mutations involving conservative amino acid changes, e.g., changes between amino acids of broadly similar molecular properties. For example, interchanges within the aliphatic group alanine, valine, leucine and isoleucine can be considered as conservative. Sometimes substitution of glycine for one of these can also be considered conservative. Other conservative interchanges include those within the aliphatic group aspartate and glutamate; within the amide group asparagine and glutamine; within the hydroxyl group serine and threonine; within the aromatic group phenylalanine, tyrosine and tryptophan; within the basic group lysine, arginine and histidine; and within the sulfur-containing group methionine and cysteine. Sometimes substitution within the group methionine and leucine can also be considered conservative. Preferred conservative substitution groups are aspartate-glutamate; asparagine-glutamine; valine-leucine-isoleucine; alanine-valine; phenylalanine-tyrosine; and lysine-arginine." Also, the specification at [0313] states that "Certain particular compounds have been described herein in various assemblies or methods of use as highly beneficial aspects of the invention. However, other analogs or derivatives thereof may be used and contemplated within the intended scope of various aspects of the invention. For example, similar bioactivity as is known for the compounds described may be achieved with modifications to the specific molecule without departing from the intended scope of such aspects. In one regard, active sites and molecular regions or shapes, etc., associated therewith may be incorporated onto other molecular chains and provide further aspects of the invention." However, the disclosure does not provide any

specific guidance regarding for ADF with regards to which substitutions, fragments, active sites and/or geometries from the great possible number of available modifications, would still retain the functional/biological activity instantly claimed. The scope is extremely broad, including any local delivery system, any effect thereof in any tissue, cell, or organism of a bioactive agent comprising apoptosis DNA factor (ADF).

3. A determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing.

The determination should include the following considerations:

a. Actual reduction to practice.

b. disclosure of drawings or structural chemical formulas.

c. Sufficient relevant identifying characteristics such as;

i. Complete structure

ii. Partial structure

iii. Physical and/or chemical properties

iv. Functional characteristics when coupled with a know or disclosed correlation between function and structure

d. Method of making the claimed invention

e. Level of skill and knowledge in the art

f. Predictability in the art

In the instant case, the level of skill is high in the biotech therapeutic area, and the knowledge in the art is low with regards to predicting the activity of substitution/fragmentation. The level of unpredictability is high with regards to the

activity/structure correlation of analogs, derivatives, substitutions and fragments of ADF, and the disclosure does not provide any guidance beyond a generic set of conservative substitutions, however, no specific structure/activity correlations have been provided. It is well understood that, with regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

Rudinger (J. Rudinger. In: Peptide Hormones, JA Parsons, Ed. (1976) 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study." (Page 6).

SIGMA (SIGMA. Designing Custom Peptides. http://www.sigma-genosys.com/peptide_design.asp (Accessed 12/16/2004), 2 pages) states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine." (Page 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility.

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable.

Berendsen (H..J.C. Berendsen. A Glimpse of the Holy Grail? Science (1998) 282, pages 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology

and one of the most demanding challenges in the new field of bioinformatics." (Page 642). Berendsen states that, "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field. (Page 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). VOET (D. Voet and J.G. Voet. Biochemistry, 2nd Edition.(1995), pages 235-241) teaches that the mutant hemoglobin HbE [Glu B8(26)β → Lys] has, "no clinical manifestations in either heterozygotes or homozygotes." (Page 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which result in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state). (Page 236).

HbS is a single point mutation, Val → Glu A3(6)β (Page 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Further, Smilek (D.E. Smilek, et al. Proc. Natl. Acad. Sci. USA (1991) 88, pages 9633-9637) teaches that a single amino acid substitution in the myelin basic protein peptide, "confers the capacity to prevent rather than induce EAE even after peptide-specific encephalitogenic T-cells have been activated." (Abstract).

Messer (W.S. Messer, "Vasopressin and Oxytocin", web document updated 4/3/2000; http://www.neurosci.pharm.utoledo.edu/MBC3320/vasopressin.htm; 5 pages) that two compounds, vasopressin [cyclo(1-6)CYIQNCPLG-NH_2] and oxytocin [cyclo(1-6)CYFQNCPRG-NH_2] differ by only two amino acids, as indicated, yet they have different functions. Vasopressin (antidiuretic hormone, ADH), "at low doses controls the resorption of water by the distal tubules of the kidneys and regulates the osmotic content of blood… [and at] high doses, ADH causes contraction of arteries (sic) and capillaries, especially those of the coronary vessels, to produce localized increases in blood pressure." (page 1).

Oxytocin, on the other hand, stimulates smooth muscle contraction in the uterus, mammary glands, and the "alveoli and larger sinuses of the mammary glands to make readily available milk" (page 1).

Further, ADH has 2 types of receptors (V1 and V2) found in vascular smooth muscle and the kidney, while oxytocin has one type of receptor found in uterine and mammary smooth muscle.

Moreover, not a single working Example of analogs/derivatives is provided.

4. For each claim drawn to a single embodiment or species, consider the above factors in regard to that embodiment or species to determined whether one of ordinary

skill in the art would recognize that the applicant was in possession of the species or embodiment at the time of filing.

In the instant case the claims are drawn to a genus of systems comprising treating a genus of conditions with a genus of bioactive agents comprising ADF and analogs or derivatives thereof (therefore, see step 5).

5. For each claim drawn to a genus, consider each of the above factors to determine whether there is disclosure of a representative number of species which would lead one skilled in the art to conclude that the applicant was in possession of the claimed invention. The number of species required to represent a genus will vary, depending on the level of skill and knowledge in the art and the variability among the claimed genus. For instance, fewer species will be required where the skill and knowledge in the art is high, and more species will be required where the claimed genus is highly variable.

In the instant case, there are no species provided for the highly variable genus of systems for local delivery of ADF analogs and ADF derivatives for treating a condition. One skilled in the art would not recognize possession of the invention at the time of filing.

Therefore, based on the analysis above, it is deemed that no sufficient written description has been provided for the claims above.

Claims 1, 21-22, 24-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a system comprising ADF (and

active analogs/derivatives thereof) for treating atherosclerosis, stenosis, restenosis, smooth muscle cell proliferation, occlusive disease does not reasonable provide enablement for the prevention thereof or enablement and prevention for any condition in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

1. Scope/ Breadth of the Claims

Determining whether the enablement requirement has been met requires analyzing the claim to determine its scope.

As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971)
The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The entire claim must be considered. The second inquiry is to determine if one skilled in the art is [sic, would have been] enabled to make and use the entire scope of the claimed invention without undue experimentation.

The instant claims are much broader than the scope of the disclosure. The disclosure is drawn to for a system for local delivery and treating atherosclerosis, stenosis, restenosis, smooth muscle cell proliferation, occlusive disease with ADF and functional analogs/derivatives thereof. The claims are drawn for a system for treating/preventing any condition with ADF and analogs/derivatives thereof.

Nature of the invention. The claims are drawn to systems for local delivery comprising ADF, analogs or derivatives thereof for the treatment/prevention of a condition which is not specified in the claim.

State of the prior art. At the time the invention was made, successful prevention of atherosclerosis, stenosis, restenosis, smooth muscle cell proliferation, occlusive disease was not routinely obtainable by those skilled in the art. This is reflected by Pickering et al. (J Clin Invest, 1993): "Smooth muscle cell proliferation in the intima of arteries is a principal event associated with vascular narrowing after balloon angioplasty and bypass surgery. Techniques for limiting smooth muscle cell proliferation, however, have not as yet yielded any therapeutic benefit for these conditions. This may reflect the present lack of sufficiently potent and specific inhibitors of smooth muscle cell proliferation". The authors go on to state that "[f]urther, approximately 40% of atherosclerotic arteries treated by balloon angioplasty develop a recurrent lesion at the site of the angioplasty procedure in the six months following this intervention. (e.g., page 724)". Further, with regards to stenosis, Chan teaches (JACC 2003) that the conventional view is that aortic stenosis a "degenerative' process, with the valve damage being a result of wear and tear. However, only a minority of elderly individuals develop aortic stenosis. Aortic stenosis, teaches Chan, is a pathogenic mechanism wherein lipoproteins are involved in multiple pathways, which lead to fibrosis and calcification (e.g., page 595). Familiar hydercholesterolemia is a factor in valvular and supravalvular aortic sclerosis.

Breadth of the claims. The claims are extremely broad, encompassing treatment and prevention of any and all conditions treatable by ADF and analogs and derivatives thereof in any animal. The broad claim 1 is not limited to treating/preventing stenosis, restenosis and so forth, but rather to treating/preventing any condition.

Working examples. No working example is disclosed in the specification.

Guidance in the specification. The specification provides little guidance regarding practice of the claimed methods. The specification refers generally to prevention of stenosis, restenosis, smooth muscle cell proliferation and occlusive disease, however does not provide any experimentation regarding administration pre-disease in order to determine prevention of the disease. There is no specific guidance regarding whether stenosis, restenosis, smooth muscle cell proliferation and occlusive disease can be preventable, e.g., in case of heart attack, coronary disease, etc. The specification does not disclose the effect, if any, of utilizing analogs/derivatives to achieve this preventive effect.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In the instant application, the claims are drawn to systems for medical intervention which can prevent/treat any condition treatable by ADF/ analog and derivative thereof. However, such interventional medical systems are not easily made and the disclosed illnesses appear to be limited to atherosclerosis, stenosis, restenosis, smooth muscle cell proliferation, occlusive disease rather than any condition treatable/preventable by ADF or analog or derivative thereof. Please note that the term “prevent” is an absolute definition, which means to stop from occurring and, thus, requires a higher standard for enablement than does “therapeutic”, especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes) – including preventing such disorders

as atherosclerosis, stenosis, restenosis, smooth muscle cell proliferation, occlusive disease (which clearly are not recognized in the medical art as being totally preventable conditions as taught by Pickering et al.). There is no way to predict what fragments/substitutions of ADF might retain the desired activity (whatever that may turn out to be), nor what conditions would be treated by such fragments/substitutions.

Amount of experimentation necessary. Besides the general expectation that it will require years of further research to develop an understanding o the complete picture in the cellular and molecular processes involved, including genetic tendencies, as well as the pathogenesis or aortic stenosis (pages 594-598) and that prevention of the development of severe aortic stenosis is a novel idea, which has not been tested. Chan also states that "[t]he time has come for such a study in patients with mild to moderate aortic stenosis (page 598)". Additionally with regards to smooth muscle proliferation, Pickering et al.state that "[f]urther, approximately 40% of atherosclerotic arteries treated by balloon angioplasty develop a recurrent lesion at the site of the angioplasty procedure in the six months following this intervention. (e.g., page 724)". It would require extensive research to understand the fundamental biology of the systems in both cases to obtain prevention, e.g., of the most severe cases. Applicants have identified an interesting peptide (ADF) which might play a role in some diseases, but essentially all of the work required to ultimately develop a treatment method has been left for others.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 21-22, 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is vague and indefinite by the phrase in line 1: “system for treating a condition by providing interventional medical care to a patient” since the disclosure does not define expressly which conditions are encompassed by the term “condition" and “interventional medical care” and therefore which set of patients/conditions are being treated is equally unclear as well. The metes and bounds of the invention are not well delineated for one skilled in the art to know if a given invention would be infringing upon the instantly claimed invention. Claims 21-22 and 24-26 are rejected as being dependent upon a rejected base claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 21-22, 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Bandman et al. (US 6,274,138).

With respect to the term “local delivery” the instant disclosure in the patent application teaches that "certain aspects of the present invention incorporate such

compounds in local delivery modalities to maximize the local potency and bioactivity at the site to be treated. For example, such would be local delivery to the site of vascular injury related to restenosis, or in the setting of treating atherosclerosis (including for example as prophylaxis of vulnerable plaque). In general, such terms of "local delivery" in this context, or terms of similar import, are herein intended to mean delivery in a manner that increases the local amount, concentration, or effect of the delivered compound in a biologically relevant manner as compared to systemic delivery, again such as via systemic IV or intramuscular injections etc. "

Bandman et al. teach the use of ADF, a derivative thereof or an analog thereof (Figure 2b). MT-MDH (mitochondrial maleate dehydrogenase) taught by Bandman et al. comprises the instantly claimed SEQ ID NO: 2-3. Bandman et al. also teaches derivatives and analogs thereof (e.g., columns 9-10). MT-MDH is expressed in tumor, proliferating, and fetal tissues; in cardiovascular, gut, nervous, and reproductive tissues; and in secretory and hematopoietic tissues (e.g., column 18, lines 21-32). Amongst the illnesses treatable with MT-MDH are included: any disorder associated with development or function of a tissue, organ or system of a subject, i.e., brain, adrenal gland, kidney, skeletal or reproductive system. Such disorders include, but are not limited to: renal tubular acidosis, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea and cerebral palsy, spinal bifida, and congenital

glaucoma, cataract, or sensorineural hearing loss. Also cystic fibrosis, glucose-galactose malabsorption syndrome, hypercholesterolemia, diabetes mellitus, diabetes insipidus, hyper- and hypoglycemia, Grave's disease, goiter, Cushing's diseases, and Addison's disease; gastrointestinal disorders including ulcerative colitis, gastric and duodenal ulcers; other conditions associated with abnormal vesicle trafficking including AIDS, allergies including hay fever, asthma and urticaria (hives); autoimmune hemolytic anemia; proliferative glomerulonephritis; inflammatory bowel disease; multiple sclerosis; myasthenia gravis; rheumatoid and osteoarthritis; scleroderma; Chediak Higashi and Sjogren's syndrome; systemic lupus erythematosus; toxic shock syndrome; traumatic tissue damage; and viral, bacterial, fungal, helminth and protozoal infections (e.g., columns 18-19). Bandman et al. teach administration by a number of routes including, but not limited to intramuscular, intraarterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, topical, sublingual, or rectal means (e.g., column 23, lines 28-34) which read upon local delivery.

Therefore, the reference is deemed to anticipate the claims above, as drafted.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 21-22, 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bandman et al. (US 6,274,138) in view of Lambert (US 5,562,922).

Bandman et al. teach the use of ADF, a derivative thereof or an analog thereof (Figure 2b). MT-MDH (mitochondrial maleate dehydrogenase) taught by Bandman et al. comprises the instantly claimed SEQ ID NO: 2-3. Bandman et al. also teaches derivatives and analogs thereof (e.g., columns 9-10). MT-MDH is expressed in tumor, proliferating, and fetal tissues; in cardiovascular, gut, nervous, and reproductive tissues; and in secretory and hematopoietic tissues (e.g., column 18, lines 21-32). Amongst the illnesses treatable with MT-MDH are included: any disorder associated with development or function of a tissue, organ or system of a subject, i.e., brain, adrenal gland, kidney, skeletal or reproductive system. Such disorders include, but are not limited to: renal tubular acidosis, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea and cerebral palsy, spinal bifida, and congenital

glaucoma, cataract, or sensorineural hearing loss. Also cystic fibrosis, glucose-galactose malabsorption syndrome, hypercholesterolemia, diabetes mellitus, diabetes insipidus, hyper- and hypoglycemia, Grave's disease, goiter, Cushing's diseases, and Addison's disease; gastrointestinal disorders including ulcerative colitis, gastric and duodenal ulcers; other conditions associated with abnormal vesicle trafficking including AIDS, allergies including hay fever, asthma and urticaria (hives); autoimmune hemolytic anemia; proliferative glomerulonephritis; inflammatory bowel disease; multiple sclerosis; myasthenia gravis; rheumatoid and osteoarthritis; scleroderma; Chediak Higashi and Sjogren's syndrome; systemic lupus erythematosus; toxic shock syndrome; traumatic tissue damage; and viral, bacterial, fungal, helminth and protozoal infections (e.g., columns 18-19). Bandman et al. teach administration by a number of routes including, but not limited to, oral, intravenous, intramuscular, intraarterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means (e.g., column 23, lines 28-34).

What is lacking in Bandman et al. is the express teaching of a local delivery system to locally deliver to the region of tissue; the use of a implantable stent and coating the stent with ADF (MT-MDH).

Lambert teaches prosthetic articles having polyurethane coatings with biologically active compounds incorporated within the interstices of the polymer. Upon long term exposure of a prosthetic article of the invention to physiological conditions, the biologically active compound is slowly released by the treated polymer. The biologically active compound is, therefore, released only at the site where it is desired, i.e., where

the prosthetic article is positioned (local delivery). Biologically active compounds include peptides, anti-inflammatory drugs, antiproliferative compounds, etc. (e.g., abstract, column 3). Substrates suitable include metallic stents, such as vascular, biliary or urethral stents, heart valves, metallic prosthesis, prosthetic joints, pacemakers, catheters, balloon coatings, ocular implants, contact lenses and the like (e.g., column 3, lines 49-54). See also Example 3, drawn to delivery of forksolin to the vascular wall in white rabbits and subsequent sample testing for stent delivery and local concentration in the removed vascular and organ tissues of the rabbits which showed that capabilities for delivering high local concentration of the drug in the vessel wall.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Bandman et al. by utilizing a coated stent for delivery, e.g., to the heart, or a coated eye implant for delivery, e.g., to the eye, and for controlling specific tissue delivery depending on the illness to be treated, as taught by Lambert. The skilled artisan would have been motivated to do so because Bandman et al. teach a wide range of therapeutic range, including, e.g., treating heart conditions such as pericarditis and myocarditis, which require local delivery to the heart, and ocular implants or eye lenses in eye conditions such as glaucoma which require local delivery to the eye. There would have been a reasonable expectation of success, given that the Lambert's delivery system is a generic system for treatment of many different illnesses with a wide variety of bioactive agents, including peptides as instantly claimed (e.g., column 3) and because Bandman et al. teach administration of the peptide ADF (SEQ ID NO: 2-3, MT-MDH) by a number of routes including, but not

limited to, oral, intravenous, intramuscular, intraarterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means (e.g., column 23, lines 28-34).

Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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